DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

1365

RECOMBINANT DNA ADVISORY COMMITTEE
REVISION OF THE NIH GUIDELINES SUBCOMMITTEE

MINUTES OF MEETING[1]

JUNE 5, 1989

The Revision of the NIH Guidelines Subcommittee, Recombinant DNA Advisory Committee, was convened at 9:00 a.m. on June 5, 1989, at the National Institutes of Health, Building 31, Conference Room 10, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. Monica Riley was Chair. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Subcommittee members:

Al W. Bourquin
Don B. Clewell
Gerard J. McGarrity
Monica Riley
Jeffrey W. Roberts
Anne K. Vidaver
Rachel E. Levinson
(Executive Secretary)

The subcommittee roster is attached.

Other National Institutes of Health staff:

Becky Lawson, OD
Jay Moskowitz, OD
Karen Riggs, OD

Others:

Elizabeth L. Anderson, Environmental Protection Agency
Ellie Clark, Environmental Protection Agency
Alan W. Dunton, Hoffmann-La Roche
Katy Gold, Environmental Protection Agency
Alan R. Goldhammer, Industrial Biotechnology Association
Anthony Gorski, National Wildlife Federation

[1]The subcommittee is advisory to the Recombinant DNA Advisory Committee, and its recommendations should not be considered as final or accepted.

Jo-Anne A. Jackson, Department of Commerce
Anthony J. Mazzaschi, Federation of American Societies for Experimental Biology
Margaret G. Mellon, National Wildlife Federation
Henry I. Miller, Food and Drug Administration
John H. Payne, Department of Agriculture
Joyce Rudick, Environmental Protection Agency
George Shibley, Department of Agriculture
Janet Shoemaker, American Society for Microbiology
Clarence E. Styron, Monsanto Company
Sue Tolin, Department of Agriculture
Lisa White, Blue Sheet
Larry Zeph, Environmental Protection Agency

Dr. Riley called the meeting of the Revision of the NIH Guidelines Subcommittee to order at 9:10 a.m.

The charge to the Subcommittee originated in the January 30, 1989 deliberations of the RAC concerning the current definition of recombinant DNA as stated in the National Institutes of Health (NIH) **Guidelines for Research Involving Recombinant DNA Molecules** (51 FR 16958). A proposal to revise the existing definition was submitted by the National Wildlife Federation (53 FR 53262). Dr. Riley briefly reviewed this proposal.

In summary, the National Wildlife Federation expressed concerns that since the first publication of the NIH Guidelines in 1976, a number of new techniques for manipulating DNA have become available. Because the classic definition of recombinant DNA is based upon end-to-end splicing of DNA fragments using restriction enzymes outside the cell, there is some question about the applicability of the current NIH Guidelines to experiments involving new methods for inserting DNA into cells when the DNA has not been subjected to recombinant techniques.

Dr. Riley asked the Subcommittee members to consider the following issues:

1. Product vs. Process - The National Wildlife Federation suggested revising the current definition of recombinant DNA to include a number of new production techniques. Dr. Riley explained that another strategy would be to evaluate hazard on the basis of characteristics of a recombinant organism.

2. Scope - Should the scope of the NIH Guidelines be enlarged or should the RAC simply seek to close any existing loopholes? For example, should the RAC consider all recombinant organisms or only certain subsets? Does Section I-B, *Definition of Recombinant DNA Molecules*, apply only to recombinant DNA molecules or also to recombinant organisms?

3. Jurisdiction - How might revision of the NIH Guidelines affect coordination of oversight with other organizations?

The Subcommittee began with an extensive discussion of various interpretations of the current scope of the NIH Guidelines. One particular question was applicability of the NIH Guidelines when recombination occurs within the cell, especially if the DNA insert has not been manipulated by recombinant techniques.

Dr. Clewell noted that there are new technologies that are distinct from recombination of DNA in solution, aided by restriction enzymes. He proposed the following revision of Section I-B:

> "In the context of these Guidelines, recombinant DNA molecules are defined as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments that can replicate in a living cell, (ii) molecules which are constructed by joining natural or synthetic DNA molecules to cellular DNA by a process not know to occur naturally,* or (iii) DNA molecules that result from the replication of those described in (i) and (ii) above."
>
> *Suggested addition is shaded.

Dr. Roberts noted that unless one assumes that the DNA must be purified, this definition might be construed to include DNA resulting from artificial insemination. Dr. Clewell responded that the process by which DNA is integrated into the ovum genome is a natural process and artificial insemination would, therefore, be excluded as one of man mimicking nature.

Dr. Vidaver said that the same question had arisen in the development of the draft guidelines being proposed by the Agricultural Biotechnology Research Advisory Committee (ABRAC). The scope of these guidelines goes beyond recombinant DNA but does not include products manufactured using natural processes.

The U.S. Department of Agriculture (USDA) draft guidelines apply to:

> "genetically modified organisms that are made through deliberate insertion, deletion, or other manipulation of DNA or RNA. These include, but are not limited to, organisms resulting from: recombinant DNA and genetic manipulations involving transfer of RNA, accomplished with or without specific molecular gene vectors; physical methods for DNA or RNA introduction into living cells, such as, electroporation, microinjection, and microprojectile procedures; cross-species cell fusion and embryo rescue techniques; and site directed mutagenesis of isolated DNA or RNA which is then reinserted into an organism."

The draft guidelines do not apply to:

> "genetically modified organisms which occur through natural reproduction or from the use of familiar, traditional breeding techniques (e.g., hand pollination, artificial insemination, superovulation, embryo transfer, and selection of somaclonal variants), when there is considerable experience and information which demonstrates that organisms

> resulting from such modifications are readily manageable, have not resulted in or are not likely to result in adverse effects on public health or the environment, and therefore, do not warrant additional controls or oversight beyond those currently in practice."

The USDA draft guidelines apply to investigators proposing to conduct agricultural research outside contained facilities. Agricultural research conducted within a laboratory, greenhouse or other containment facility is still conducted under the NIH Guidelines.

Dr. Henry Miller of the Food and Drug Administration emphasized that the amount of regulation and scrutiny a proposed experiment must undergo should be commensurate with its degree of risk. He claimed that the USDA guidelines focus on the process by which an organism is constructed rather than the risks presented by the product.

According to Dr. Miller, the **CDC/NIH Biosafety in Microbiological and Biomedical Laboratories Handbook** represented a more appropriate model for regulation in that it is totally risk-based as opposed to process-based. While the NIH Guidelines originated at time when it was thought that recombinant DNA might pose unique hazards, now that is known not to be the case. Therefore, the RAC ought to move away from a process-based review strategy, Dr. Miller concluded.

Dr. Riley answered that the charge to the RAC and to the Subcommittee is to review research involving recombinant DNA and any associated hazards and that the intent behind the current scope of the NIH Guidelines is based on the original definition.

Dr. Roberts noted that it is worth keeping in mind that the newer technologies in question provide the means for <u>introducing</u> DNA into cells, rather than <u>constructing</u> DNA. Changing the definition of recombinant DNA in order to cover these methods may represent a rather drastic and, perhaps, undesirable change in the scope of the NIH Guidelines, in Dr. Roberts view. He added that all of the new techniques are already covered because most, if not all, of the newly-introduced DNA is the product of recombinant technology.

Dr. Riley raised the question of applicability of the NIH Guidelines when recombinant DNA is used for selection but the vector is then cut out of the final construct. Drs. Vidaver and Clewell noted that the Working Group on Transgenic Animals concluded that such constructs are not covered (See minutes of meeting, March 28, 1988).

Dr. Margaret Mellon, National Wildlife Federation representative, emphasized the following three points:

1. It is important to be certain of the validity of the assumption that all DNA is modified prior to introduction, if this is to be the sole determinant for coverage under the NIH Guidelines.

2. If so, this assumption and interpretation of the NIH Guidelines should be made explicit.

3. If all of these technologies are covered, is there a downside to this interpretation?

On balance, updating the current definition to include new technologies seems worthwhile, concluded Dr. Mellon.

In response to Dr. Mellon's first point, Dr. Roberts said that there are experiments where non-recombinant DNA is used, for example, the recently-reported work on *in vitro* genetic additions to sperm. However, most such experiments involve bulk DNA, which poses little risk because this: (1) mimics a natural process, and (2) is not an efficient method for introducing specific traits.

The Executive Secretary brought to the participants' attention the wording adopted by the Working Group on Transgenic Animals to cover recombinant DNA or "DNA derived therefrom."

Dr. Mellon questioned the utility of basing a determination of risk on the presence or absence of a covalent bond. In other words, should the fact that DNA has been altered outside the cell rather than inside following mechanical introduction determine applicability of the Guidelines? Instead, she stated, the novelty of the product should be the principal concern.

For the purposes of clarification, Dr. Clewell reiterated that a gene characterized and isolated without recombinant technology could be inserted into a cell mechanically and would not be covered under the current definition of recombinant DNA in the Guidelines. Dr. Roberts agreed that this is possible but hypothesized that it would happen only in the case of an attempt to avoid having to comply with the NIH Guidelines. Dr. Vidaver suggested that, in fact, these newer methods may have been developed for just that purpose.

Dr. McGarrity reminded Subcommittee members that the NIH Guidelines have been evolving gradually in the direction of simplifying procedures and putting more oversight into the jurisdiction of the Institutional Biosafety Committees (IBCs). However, the proposal from the National Wildlife Federation might

result in the addition of restrictions on investigators, particularly with respect to transgenic animals. Reviewing any technology that results in the stable integration of DNA into a genome might expand significantly the entire scope of the Recombinant DNA Advisory Committee (RAC) with respect to safety. He concurred with Dr. Roberts that in his experience, most such experiments are covered already by virtue of insertion of recombinant DNA.

Dr. McGarrity emphasized that the key charge to the RAC is providing advice to the NIH Director and to the IBCs on the safe use of recombinant DNA. He asked if anyone present could envision a new class of hazardous experiments that might result from the technological advances under discussion. Conceivably, such concerns could be addressed by the RAC under an expanded version of the NIH Guidelines. For example, they might be called "Guidelines for Research Involving Recombinant DNA and Related Technologies."

Dr. Mellon agreed with such a concept. She explained her view that expanding the scope would not necessarily increase the burden of oversight on investigators and on the RAC because most experiments would be exempt. Instead, such a revision would enhance the NIH Guidelines' scientific consistency. Dr. McGarrity noted that a new categorization of risks could be an enormous task, albeit necessary.

Reiterating Dr. McGarrity's question, Dr. Riley asked Subcommittee members for examples of hazardous experiments that would not be covered if all methods for DNA introduction were included in the definition of recombinant.

Dr. Tolin related an experiment reviewed by a special NIH committee that involved an organism that had been constructed so that there were no splice junctions in the final product. The RAC had concluded that this experiment was not covered. However, she noted, this had no bearing on the question of whether or not a hazardous organism had been created.

The Executive Secretary read the following quote from the March 28, 1988, minutes of the Working Group on Transgenic Animals:

> "This section covers experiments involving whole animals, both those in which the animal's genome has been altered by stable introduction of **recombinant DNA, or DNA or RNA derived therefrom**, into the germ line (transgenic animals) and experiments involving viable recombinant-DNA-modified microorganisms tested on whole animals."

Dr. Vidaver remarked that the meaning of "stable introduction" is still left open to interpretation. In the Montana case for

example, the vector and the splice junction dropped out. In other cases, the inserted gene is lost over time.

Dr. Riley asked if addition of the phrase "DNA derived therefrom" would cover concerns raised earlier by Dr. Roberts, to which he responded affirmatively.

Dr. Clewell had some residual reservations about an implied assumption that only recombinant DNA would be inserted. For example, efforts initiated under the aegis of the human genome project will make it possible for investigators to identify and isolate chromosomal segments for insertion without using recombinant technology.
Dr. McGarrity agreed that this is a likely prospect.

Dr. Riley urged Subcommittee members to reexamine Dr. Clewell's suggestion with the intent of closing potential gaps in oversight. Dr. Bourquin raised the issue of natural processes falling under this scheme, to which Dr. Vidaver responded that techniques such as artificial insemination could be exempted out. Drs. Clewell and Roberts agreed that the newer technologies do not pose new risks. Rather, increased hazard is more likely to be associated with the classical methods that do not offer the same fine control and certainty about the effects of genetic manipulation as the more precise recombinant DNA techniques.

Dr. Mellon argued that the reason new techniques are being developed is that older methods are proving unsatisfactory, e.g., in plant biotechnology. Dr. Roberts agreed with her in part, but added that most efficient genes must be engineered, such as herbicide resistance.

The question was raised as to the applicability of the NIH Guidelines to DNA produced using the polymerase chain reaction (PCR). Dr. Riley asked participants to consider two issues: (1) what <u>is</u> recombinant DNA, and (2) does the definition cover DNA that replicates in a target cell, or is it confined to DNA replicating in a plasmid or a virus?

Dr. McGarrity suggested that a broader base of information regarding hazards that may or may not be associated with various techniques would enhance this discussion.

In support of this idea, Dr. Clewell noted that the rate at which DNA can be taken up in transgenic animals, for example, is much more efficient than originally predicted. This kind of information is necessary in order to evaluate the need for revisions to the NIH Guidelines.

Dr. Mellon informed Subcommittee members that the National Academy of Sciences is conducting a study that will examine many of these issues.

Dr. Miller asked if there was any sentiment for looking at how the NIH Guidelines might be revised so as to become more product- than process-based. Dr. Bourquin answered that the RAC had made a decision to emphasize product risks, not process, in the Montana case. However, Dr. Sue Tolin of the USDA explained that in this case the RAC had deferred judgement to a special committee. The committee concluded that the organism did not include recombinant DNA, having used a transposon that did not transfer any DNA in excess of the desired sequence.

Expanding on Dr. Miller's proposal, Dr. Bourquin noted that in considering any potential harm associated with newer techniques, one must recognize that even natural processes may have harmful effects. Assessment of the potential human health effects of products may be preferable to pursuing stopgap measures ad infinitum.

Dr. Riley stated that the study must relate to the mission of the RAC, which does not have as its charge the review of all potentially hazardous biological experiments. She observed a consensus among participants on the need for focus and more information on the nature of hazards that should be covered by the Guidelines. However, such experiments involving DNA manipulation are in the bailiwick of the RAC. As Chair, Dr. Riley solicited a motion from Subcommittee members, noting an assumption that the focus would remain on laboratory-contained research.

Dr. McGarrity mentioned that this would be more of a survey of potential hazards associated with but not limited to particular techniques.

Dr. Bourquin presented the following motion, which was seconded by Dr. Vidaver.

Motion:

> "This Subcommittee recommends that the RAC institute a survey for the potential hazards of practices involving technologies which are related to recombinant DNA but which are not covered under the NIH Guidelines."

It was agreed that such a survey would require some discussion of what is covered by the current definition of recombinant DNA.

Dr. Miller presented an alternative study that would include an assessment of enlarging the scope of the NIH Guidelines to encompass non-recombinant organisms. Dr. Riley responded that this would be rather different than the motion on the table.

Dr. Mellon said that the National Wildlife Federation proposal was not intended to enlarge the purview of the RAC. Dr. McGarrity stated that such a change would belong in the *Purpose* section of the NIH Guidelines, rather than in the definition. Such revisions might be considered by the NIH Director, based on the results of the survey.

Dr. Clewell offered an alternative motion for discussion:

Motion:

> "This Subcommittee recommends that the Recombinant DNA Advisory Committee institute a study on the extent to which new techniques for introducing foreign DNA into living cells without the use of recombinant DNA methodology pose potential biohazards."

Dr. Bourquin withdrew his earlier motion and instead, suggested amending Dr. Clewell's motion by inserting the phrase "pose unique threats to public health or to the environment."

The original motion was passed, without amendment, by a vote of 5 in favor, none opposed and no abstentions.

Dr. Riley then asked for a sense of the Subcommittee on expanding the reference to replication by including any foreign DNA stably integrated into the genome of a viable cell that is replicating.

Dr. Roberts stated that the current definition is quite restrictive but that a more general definition would draw in naturally-occurring processes. The narrow interpretation originally was adopted because this notion had been viewed as undesirable.

The Subcommittee concluded that these deliberations would be well served by the results of a survey including applications of non-recombinant DNA.

Dr. Riley adjourned the meeting at 12:10 p.m.

Respectfully submitted,

Rachel E. Levinson
Executive Secretary
Revision of the NIH Guidelines Subcommittee

I hereby certify that, to the best of my knowledge, the foregoing Minutes and Attachment are accurate and complete.

7/5/89
Date

Monica Riley, Ph.D
Chair
Revision of the NIH Guidelines Subcommittee
Recombinant DNA Advisory Committee

Attachment

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